# EXHIBIT 9

# GLP-1-Based Therapy for Diabetes: What You Do Not Know Can Hurt You

According to the *Oxford Dictionary of Proverbs*, the oldest written version of the saying "What you don't know can't hurt you" comes from *Petit Palace*, written in 1576 by G. Pettie: "So long as I know it not, it hurteth mee not."

In this issue of *Diabetes Care*, Drucker et al. (1) conclude that the safety profile of the newly available glucagon-like peptide 1 (GLP-1) class of drugs is favorable in comparison to their benefits as therapy, and the class of drugs might be considered as next in line after metformin for treatment for type 2 diabetes. The purpose of this counterpoint is to suggest such a conclusion is premature. History has taught us that enthusiasm for new classes of drugs, heavily promoted by the pharmaceutical companies that market them, can obscure the caution that should be exercised when the long-term consequences are unknown. Of perhaps greatest concern in the case of the GLP-1–based drugs, including GLP-1 agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, is preliminary evidence to suggest the potential risks of asymptomatic chronic pancreatitis and, with time, pancreatic cancer.

The GLP-1–related drugs arrived in clinical practice with much fanfare and anticipation. As summarized in the article by Drucker et al., it is a class of drugs that has potential benefits in the treatment of type 2 diabetes. The concept of gut-related factors that enhance glucose-mediated insulin secretion, the incretin effect, has been recognized for many years (2). Once it was demonstrated that an intravenous infusion of GLP-1 could decrease blood glucose concentrations in patients with type 2 diabetes, the race was on to exploit the properties of this action. Many millions of dollars have been invested by the pharmaceutical industry in developing products, the first of which are now in clinical practice. Many millions of dollars therefore are now also invested to market the new agents, reminiscent of the period that followed the launch of the most recent new class of drugs for type 2 diabetes, the peroxisome proliferator–activated receptor-γ (PPAR-γ) agonists.

The parallels with the launch of the PPAR-γ agonist and GLP-1 mimetic class of drugs is worthy of comparison. GLP-1 and PPAR-γ agonist therapies were developed as novel approaches for the treatment of type 2 diabetes building on elegant studies of basic physiology. There was a clear and rational initial therapeutic target with both classes of drugs: insulin resistance for PPAR-γ agonists and enhanced glucose-mediated insulin secretion for the GLP-1 class of drugs.

Before either class of drugs reached market, possible additional attractive attributes were identified mostly through rodent studies. In the case of the PPAR-γ agonist drugs, the most widely anticipated additional benefit was decreased vascular disease because of favorable effects of the drug class on risk factors for vascular disease supported by murine studies reporting protection against ischemic heart disease (3). Not until the European regulatory authorities required appropriately powered studies to demonstrate vascular benefit to support these claims were such studies undertaken (4,5). The results, despite optimistic interpretation by the sponsors, showed little if any cardiovascular benefit that could not have been a consequence of glucose lowering with some suggestion that the net effects of some agents might be harmful on vascular disease (6).

History may be repeating itself with the GLP-1 class of drugs. Putative benefits of GLP-1 mimetic therapy, in addition to enhanced insulin secretion, have been proposed and often arise from rodent studies. These benefits include cardiovascular protection against ischemia and prevention and/or reversal of the defect in β-cell mass that is characteristic of type 2 diabetes (7,8). While these attributes would be highly desirable, there is no current data available to support either of these claims in humans, and recent studies imply that the beneficial effects on β-cell mass in part may be an artifact of studies in juvenile rodents (9–11).

What is the risk profile of GLP-1 drugs? Perhaps the parallel with the PPAR-γ receptor agonists is again worth considering. The receptors targeted by each drug—the PPAR-γ receptor and the GLP-1 receptor, respectively—are widely distributed in numerous tissues with as yet ill-defined roles. As such, it is not surprising when unintended consequences of chronic receptor activation emerge. Potential signals have already emerged in the case of GLP-1 mimetic therapy, one is pancreatitis (12–14) and another, which is currently confined to rodents studies, is thyroid cancer (11).

Pancreatitis first emerged as a potential side effect of therapy with exenatide, initially reported as case reports (12–14) and subsequently by numerous reports made through the U.S. Food and Drug Administration (FDA) adverse reporting mechanism. The Amylin Corporation's response to this putative link has been to suggest that it was a consequence of guilt by association rather than a drug effect since pancreatitis is more common in individuals with obesity and type 2 diabetes (15). The Amylin Corporation also suggested that since no mechanism is known to link GLP-1 mimetic therapy to pancreatitis, the association is unlikely causal. Pancreatitis was also seen in clinical studies of the GLP-1 agonist liraglutide (16). More recently, the FDA has reported more than 80 documented cases of pancreatitis in patients treated with sitagliptin, a DPP-4 inhibitor (17). It is also Merck's position that the reported pancreatitis with sitagliptin therapy is due to the increased risk of pancreatitis in type 2 diabetes rather than a consequence of drug therapy (18), mimicking the Amylin Corporation position.

In post-marketing studies sponsored by the marketing companies, no increased signal for acute pancreatitis has been identified (19,20). However, the duration of treatment in those studies is typically short, the quality of the patient follow-up is questionable, and evidence that prescriptions were actually taken is absent. Nonetheless, on the basis of the available clinical information, we agree with the conclusions of Drucker et al. (1) that the data required to link GLP-1 therapy and acute pancreatitis is currently incomplete. However, in the context of a new class of medical therapy, the proverb "What you do not know cannot hurt you" clearly does not apply. We feel that enough preliminary evidence has accumulated to suggest that there is a plausible risk that long-term recipients of GLP-1–based therapy may develop asymptomatic chronic pancreatitis (Fig. 1), and worse, subsequently a minority of individuals

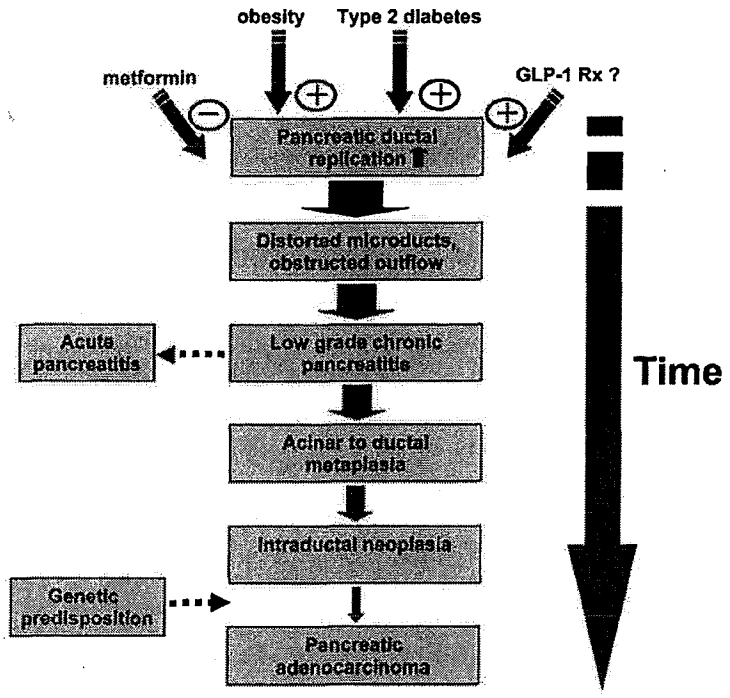


**Figure 1**—*Theoretical model to explain currently available observations with increased risks for pancreatic cancer in individuals with obesity and type 2 diabetes, a risk that is decreased by metformin treatment and theoretically may be increased by GLP-1–based treatment.*

treated by this class of drugs may develop pancreatic cancer.

The incidence of both pancreatitis and pancreatic cancer is increased in individuals with obesity and/or type 2 diabetes (21–23), although the underlying mechanisms are not well understood (Fig. 1). One potential link is the frequency of pancreatic duct replication, which is increased in humans with obesity and/or type 2 diabetes (24). It is not known why ductal turnover is increased with obesity and type 2 diabetes. One of the consequences of chronically increased ductal replication can be distortion of small pancreatic ducts with subsequent outflow obstruction of pancreatic enzymes providing a plausible mechanistic link between obesity and/or diabetes and the increased risk for pancreatitis. Moreover, increased ductal replication and chronic pancreatitis are both risk factors for pancreatic cancer (21). Given the apparent signal of occasional acute pancreatitis in patients treated with GLP-1–based therapy, how do we reassure ourselves that asymptomatic chronic pancreatitis is not also induced in some patients?

The most significant challenge is limited access to the human pancreas. To date there are also limited studies available in rodents. Koehler et al. (25) reported no evidence of GLP-1–induced pancreatitis based on RNA levels in mice, but histology was not provided and numbers of mice in most experimental groups ($n \sim 5$) were perhaps small to conclude a negative finding. On the other hand, both sitagliptin and exenatide have been shown to induce pancreatitis in rats (26,27). Sitagliptin administered to the high-fat–fed human islet amyloid polypeptide (HIP) rat model of type 2 diabetes amplified the increased pancreatic duct cell replication present in that model (27). Moreover, sitagliptin therapy induced acinar to ductal metaplasia in ~30% of treated animals. Acinar to ductal metaplasia follows increased ductal replication in the morphological progression of chronic pancreatitis to pancreatic adenocarcinoma (Fig. 1) (15).

Was this finding a quirk of the HIP rat model of type 2 diabetes? Perhaps, but it is of interest to note that increased ductal replication in the HIP rat model of type 2 diabetes compared with wild-type rats reproduces that which was observed in humans with type 2 diabetes compared with nondiabetic individuals (24). Moreover, metformin therapy in the HIP rat had the opposite effect of sitagliptin, decreasing the frequency of ductal replication. Therefore, arguably the HIP rat successfully predicts both the increased risk of pancreatitis with sitagliptin and the decreased risk of pancreatic cancer in individuals with type 2 diabetes treated with metformin (28).

Exenatide therapy given over 75 days to rats induced low-grade chronic pancreatitis (26). Again, as in the case of the sitagliptin-treated HIP rats, there was no discernable clinical manifestation of the low-grade pancreatitis induced by exenatide, with the rats in no apparent pain. If GLP-1 mimetic therapy with either GLP-1 mimetic therapy or DPP-4 inhibition induces asymptomatic chronic pancreatitis in rats, how do we know that a similar effect is not present in humans using these therapies? If GLP-1–based therapy causes low chronic pancreatitis, why was this not established in toxicology studies? One possibility is that since ductal replication is increased with obesity or type 2 diabetes (24), and GLP-1 may amplify this, studies in lean nondiabetic animals may have had a limited propensity to GLP-1–induced pancreatitis. Also, most toxicology studies are carried out in juvenile mice in which the pancreas is still growing. Enhanced ductal replication under these circumstances may simply lead to pancreas growth as observed by Koehler et al. (25) rather than distortion of the architecture of the acinar to duct relationship, thus predisposing to chronic pancreatitis.

While low-grade asymptomatic pancreatitis in and of itself as a result of GLP-1–based therapy would not be a cause for major concern, the problem is that it represents a risk for pancreatic cancer (21). The risk for developing pancreatic cancer increases with the duration of chronic pancreatitis (22). Because medications for type 2 diabetes may be taken for many years, if GLP-1–based therapy did induce low-grade asymptomatic pancreatitis, there is a real concern that such a therapy might increase the risk for pancreatic cancer. Even if this is a relatively small risk (which we do not know), how many of us practicing physicians would choose a therapeutic strategy for ourselves with insight into the potential for this risk? Since metformin has been shown to decrease the risk of pancreatic cancer, at the least we would suggest that GLP-1–based medications should be reserved for patients taking metformin.

In conclusion, we believe it is premature to conclude that the GLP-1 class of drugs has been established as having a good safety profile and is appropriate for a relatively early choice of therapy for type 2 di-

abetes. There are grounds for concern that the GLP-1 class of drugs may induce asymptomatic pancreatitis and, over time in some individuals, induce pancreatic cancer. At present, these concerns are based on limited data. However, the implications of the data are sufficiently serious that continuing to promote this class of drugs without establishing clear experimental evidence to permit the concern to be rejected is irresponsible. Moreover, arguably patients prescribed these drugs should be made aware of the potential risks of pancreatic cancer. Otherwise, we collectively subscribe to the proverb "What you do not know cannot hurt you" and, in the case of new drug therapy, this proverb has already been shown to be flawed.

PETER C. BUTLER, MD
SARAH DRY, MD
ROBERT ELASHOFF, PHD

From the Larry L. Hillblom Islet Research Center, Department of Pathology and Department of Biomathematics, University of California, Los Angeles, Los Angeles, California.
Corresponding author: Peter Butler, pbutler@mednet.ucla.edu.
DOI: 10.2337/dc09-1902


**Acknowledgments**— No potential conflicts of interest relevant to this article were reported.

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# EXHIBIT 10

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1 2 3 4 5 6 7 8 9 10 DOW/DOW 15 14 13 12 11

Two Volume Set ISBN 978-0-07174889-6; MHID 0-07-174889-X
Volume 1 ISBN 978-0-07-163244-7; MHID 0-07-163244-1
Volume 2 ISBN 978-0-07-174887-2; MHID 0-07-174887-3
DVD ISBN 978-0-07-174888-9; MHID 0-07-174888-1

**FOREIGN LANGUAGE EDITIONS**

**Arabic** (13e): McGraw-Hill Libri Italia srl (1996)
**Albanian**(17e): Tabernakul Publishing, Skopje, Macedonia
**Chinese Long Form** (15e): McGraw-Hill International Enterprises, Inc., Taiwan
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**French** (16e): Medecine-Sciences Flammarion, Paris, France
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**Greek** (17e): Parissianos, S.A., Athens, Greece
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**Korean** (17e): McGraw-Hill Korea, Inc., Seoul, Korea
**Macedonian** (17e): Tabernakul Publishing, Skopje, Macedonia
**Polish** (17e): Czelej Publishing Company, Lubin, Poland
**Portuguese** (17e): McGraw-Hill Interamericana Editores, SA de C.V. Mexico City, Mexico
**Romanian** (17e): Editura All, Bucharest, Romania
**Serbian** (15e): Publishing House Romanov, Bosnia & Herzegovina, Republic of Serbska
**Spanish** (17e): McGraw-Hill Interamericana Editores, SA de C.V. Mexico City, Mexico
**Turkish** (17e): Nobel Tip Kitabevleri, Ltd., Istanbul, Turkey
**Vietnamese** (15e): McGraw-Hill Education (Asia), Singapore

This book was set in Minion Pro by Cenveo Publisher Services. The editors were James F. Shanahan and Kim J. Davis. The production managers were Phil Galea and John Williams; production assistance was provided by Rajni Pisharody at Cenveo Publisher Services. The index was prepared by Susan Hunter and Ann Blum. The text designer was Alan Barnett; cover design was by Anthony Landi. RR Donnelley was printer and binder.

**Library of Congress Cataloging-in-Publication Data**

Harrison's principles of internal medicine.—18th ed. / editors, Dan L. Longo ... [et al.]. p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-07-174889-6 (set)—ISBN 978-0-07-163244-7 (vol. 1)—ISBN 978-0-07-174887-2 (vol. 2)
1. Internal medicine. I. Longo, Dan L. (Dan Louis), 1949- II. Harrison, Tinsley Randolph, 1900-1978. III. Title: Principles of internal medicine.
[DNLM: 1. Internal Medicine. WB 115 H322 2011]
RC46.H333 2008
616—dc22 2008053547

# CHAPTER 93

# Pancreatic Cancer

Irene Chong
David Cunningham

Pancreatic cancer is the fourth leading cause of cancer death in the United States and is associated with a poor prognosis. Endocrine tumors affecting the pancreas are discussed in Chap. 350. Infiltrating ductal adenocarcinomas, the subject of this chapter, account for the vast majority of cases and arise most frequently in the head of pancreas. At the time of diagnosis 85–90% of patients have inoperable or metastatic disease, which is reflected in the 5-year survival rate of only 5% for all stages combined. An improved 5-year survival of up to 20% may be achieved when the tumor is detected at an early stage and when complete surgical resection is accomplished.



## EPIDEMIOLOGY

Pancreatic cancer represents 3% of all newly diagnosed malignancies in the United States. The most common age group at diagnosis is 60–79 years for both sexes. Pancreatic cancer will be diagnosed in approximately 43,140 patients and account for 36,800 deaths in 2010. Over the past 30 years, 5-year survival rates have not improved substantially.

## RISK FACTORS

Cigarette smoking may be the cause of up to 20–25% of all pancreatic cancers and is the most common environmental risk factor for this disease. Other risk factors are not well established due to inconsistent results from epidemiological studies, but include chronic pancreatitis and diabetes. It is difficult to evaluate whether these conditions are causally related, or develop as a consequence of cancer. Alcohol does not appear to be a risk factor unless excess consumption gives rise to chronic pancreatitis.

## GENETIC CONSIDERATIONS

Pancreatic cancer is associated with a number of well-defined molecular hallmarks. The most frequent genetic aberrations comprise *KRAS* mutations, mostly affecting codon 12, which are observed in 60–75% of pancreatic cancers. The tumor-suppressor genes *p16*, *p53*, and *SMAD4* are frequently inactivated; the *p16* gene locus on chromosome 9p21 is deleted in up to 95% of tumors, the *p53* gene is inactivated by mutation or deleted in 50–70% of tumors, and the *SMAD4* gene is deleted in 55% of pancreatic tumors. Furthermore, *SMAD4* gene inactivation is associated with poorer survival in patients with surgically resected pancreatic adenocarcinoma. *IGF-1R* and focal adhesion kinase (*FAK*) interact to promote cell proliferation and survival, and their simultaneous inhibition synergistically inhibits pancreatic cell growth. Overexpression and/or aberrant activation of *c-Src* is frequently observed, which results in cell adhesion, enhanced migration, invasion, and cell proliferation. Survivin is overexpressed in more than 80% of pancreatic tumors, which results in resistance to apoptosis, and genomic sequencing has identified *PALB2* as a susceptibility gene for pancreatic cancer.

Up to 16% of pancreatic cancers are thought to be inherited. This occurs in three separate clinical settings: (1) familial multi-organ cancer syndromes, (2) genetically driven chronic diseases, and (3) familial pancreatic cancer with as yet unidentified genetic abnormalities, which comprise the largest proportion of inherited pancreatic cancer. The familial multi-organ cancer syndromes consist of Peutz-Jeghers syndrome, familial atypical multiple mole melanoma (FAMMM), familial breast-ovarian cancer associated with germline mutations in *BRCA1* and *BRCA2*, hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), and Li-Fraumeni syndrome. Peutz-Jeghers, associated with mutations in the *STK11* gene, carries the highest lifetime risk of pancreatic cancer with a relative risk of approximately 132-fold above that of the general population. Genetically driven chronic causes of pancreatic cancer include hereditary pancreatitis, cystic fibrosis, and ataxia telangiectasia. The absolute number of affected first-degree relatives is also correlated with increased cancer risk, and patients with at least two first-degree relatives with pancreatic cancer should be considered to have familial pancreatic cancer until proven otherwise.

## SCREENING AND EARLY DETECTION

Screening is not routinely recommended as putative tumor markers such as Ca 19-9 and CEA have insufficient sensitivity, and computed tomography (CT) has inadequate resolution to detect pancreatic dysplasia. Endoscopic ultrasound (EUS) is a more promising screening tool, and preclinical efforts are focused on identifying biomarkers that may detect pancreatic cancer at an early stage. Consensus practice recommendations based largely on expert opinion have chosen a threshold of >tenfold increased risk for developing pancreatic cancer to select individuals who may benefit from screening. This includes family members with ≥3 first-degree relatives with pancreatic cancer, and patients with FAMMM, Peutz-Jeghers syndrome, or hereditary pancreatitis.

## CLINICAL FEATURES

### CLINICAL PRESENTATION

Obstructive jaundice occurs frequently when the cancer is located in the head of pancreas. This may be accompanied by symptoms of abdominal discomfort, pruritus, lethargy, and weight loss. Less common presenting features include epigastric pain, backache, new onset diabetes mellitus, and acute pancreatitis caused by pressure effects on the pancreatic duct. Nausea and vomiting, resulting from gastroduodenal obstruction, may also be a symptom of this disease.

### PHYSICAL SIGNS

Patients can present with jaundice and cachexia, and scratch marks may be present. Of patients with operable tumors 25% have a palpable gall bladder (Courvoisier's sign). Physical signs related to the development of distant metastases include hepatomegaly, ascites, left supraclavicular lymphadenopathy (Virchow's node), and periumbilical lymphadenopathy (Sister Mary Joseph's nodes).

## DIAGNOSIS

### DIAGNOSTIC IMAGING

Patients who present with clinical features suggestive of pancreatic cancer undergo imaging to confirm the presence of a tumor, and to establish whether the mass is likely to be inflammatory or malignant in nature. Other imaging objectives include the local and distant staging of the tumor, which will determine resectability and provide prognostic information. Dual phase, contrast-enhanced spiral CT is the imaging modality of choice (Fig. 93-1). It provides accurate

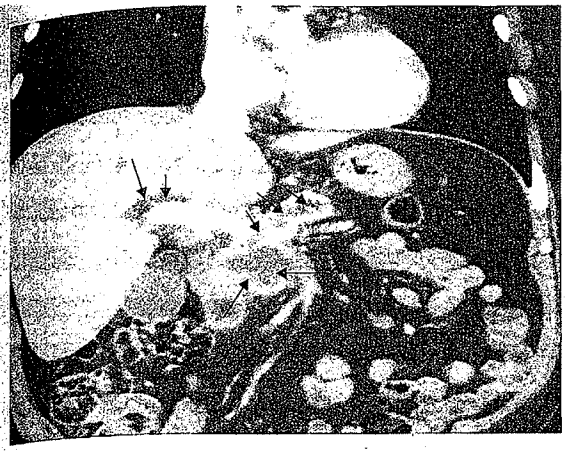


Figure 93-1 Coronal CT showing pancreatic cancer and dilated intrahepatic and pancreatic ducts (arrows).

visualization of surrounding viscera, vessels, and lymph nodes, thus determining tumor resectability. Intestinal infiltration, and liver and lung metastases are also reliably depicted on CT. There is no advantage of magnetic resonance imaging (MRI) over CT in predicting tumor resectability, but selected cases may benefit from MRI to characterize the nature of small indeterminate liver lesions and to evaluate the cause of biliary dilatation when no obvious mass is seen on CT. Endoscopic retrograde cholangiopancreatography (ERCP) is useful for revealing small pancreatic lesions, identifying stricture or obstruction in pancreatic or common bile ducts, and facilitates stent placement (Fig. 93-2). Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method for accurately depicting the level and degree of bile and pancreatic duct dilatation. EUS is highly sensitive in detecting lesions less than 3 cm in size, and is useful as a local staging tool for assessing vascular invasion and lymph node involvement. Positron-emission tomography with fluorodeoxyglucose positron emission tomography (FDG-PET) should be considered before surgery or radical chemoradiotherapy (CRT), as it is superior to conventional imaging in detecting distant metastases.

### TISSUE DIAGNOSIS AND CYTOLOGY

Preoperative confirmation of malignancy is not always necessary in patients with radiological appearances consistent with operable pancreatic cancer. However, EUS-guided fine-needle aspiration is the technique of choice when there is any doubt, and also for use in patients who require neoadjuvant treatment. It has an accuracy of approximately 90% and has a smaller risk of intraperitoneal dissemination compared with the percutaneous route. Percutaneous biopsy of the pancreatic primary or liver metastases is only acceptable in patients with inoperable or metastatic disease. ERCP is a useful method for obtaining ductal brushings, but the diagnostic value of pancreatic juice sampling is only in the order of 25–30%.

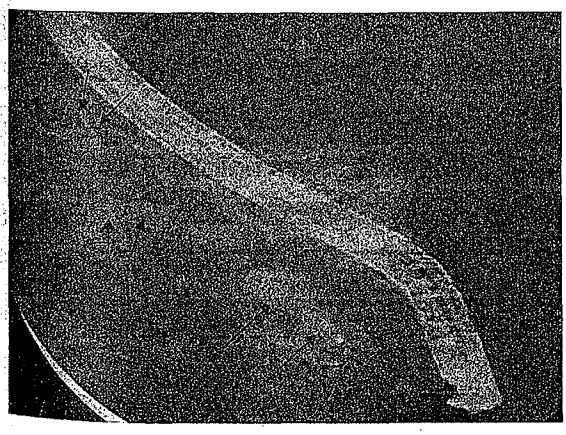


Figure 93-2 ERCP showing contrast in dilated pancreatic duct (arrows).

### SERUM MARKERS

Tumor-associated carbohydrate antigen 19-9 (CA 19-9) is elevated in approximately 70–80% of patients with pancreatic carcinoma, but is not recommended as a routine diagnostic or screening test as its sensitivity and specificity are inadequate for accurate diagnosis. Preoperative CA 19-9 levels correlate with tumor stage, and postresection CA 19-9 level has prognostic value. It is an indicator of asymptomatic recurrence in patients with completely resected tumors and is used as a biomarker of response in patients with advanced disease undergoing chemotherapy. A number of studies have established a high pretreatment CA 19-9 level as an independent prognostic factor.

### STAGING

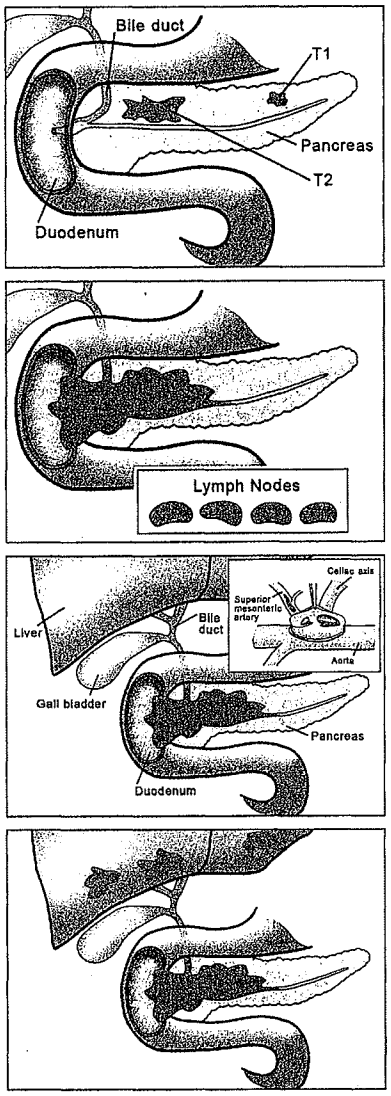
The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging of pancreatic cancer takes into account the location and size of the tumor, the involvement of lymph nodes, and distant metastasis. This information is then combined to assign a stage (Fig. 93-3). From a practical standpoint, patients are grouped according to whether the cancer is resectable, locally advanced (unresectable, but without distant spread), or metastatic.

## TREATMENT Pancreatic Cancer

**RESECTABLE DISEASE** Approximately 10% of patients present with localized nonmetastatic disease that is potentially suitable for surgical resection. Approximately 30% of patients have R1 resection (microscopic residual disease) following surgery. Those who undergo R0 resection (no microscopic or macroscopic residual tumor), and who receive adjuvant treatment have the best chance of cure, with an estimated median survival of 20–23 months and a 5-year survival of approximately 20%. Outcomes are more favorable in patients with small (< 3cm), well-differentiated tumors, and lymph node-negative disease.

Patients should have surgery in dedicated pancreatic centers that have lower postoperative morbidity and mortality rates. The standard surgical procedure for patients with tumors of the pancreatic head or uncinate process is a pylorus-preserving pancreaticoduodenectomy (modified Whipple's procedure). The procedure of choice for tumors of the pancreatic body and tail is a distal pancreatectomy, which routinely includes splenectomy.

Postoperative treatment, either chemotherapy or CRT, improves long-term outcomes in this group of patients. Adjuvant chemotherapy, comprising six cycles of fluorouracil (5FU) and folinic acid (FA) or gemcitabine, is common practice in Europe based on data from three randomized controlled trials (Table 93–1): Results from the European Study Group for Pancreatic Cancer 1 trial (ESPAC-1) revealed a median survival improvement from 14.7 months with surgery alone to 20.1 months with surgery plus adjuvant 5FU/FA, and patients did not benefit from CRT in this study. The Charité Onkologie trial (CONKO 001) found that the use of gemcitabine after complete resection significantly delayed the development of recurrent disease compared with surgery alone. The ESPAC-3 trial, which investigated the benefit of adjuvant 5FU/FA versus gemcitabine,




| AJCC Stage | TNM Stage | Extent of Tumor | 5 year Survival | Stage at Presentation (14% Unknown) |
|---|---|---|---|---|
| | T1/N0 | Limited to pancreas ≤ 2cm | | |
| I | | | 20% | 7% |
| | T2/N0 | Limited to pancreas > 2cm | | |
| II | T3 or N1 | Beyond pancreas or regional lymph node metastases | | |
| | | | 8% | 26% |
| III | T4 any N | Involves celiac axis or superior mesenteric artery | | |
| IV | M1 | Distant metastases | 2% | 53% |

**Figure 93-3** Staging of pancreatic cancer, and survival according to stage. *(Illustration by Stephen Millward.)*

**TABLE 93-1** Phase III Studies of Adjuvant Chemotherapy in Resected Pancreatic Cancer

| Study | Comparator Arm | Patient Number | Survival | |
|---|---|---|---|---|
| | | | PFS/DFS (months) | Median survival (months) |
| ESPAC 1 Neoptolemos et al. (2004) | Chemotherapy (Folinic acid + bolus 5FU) vs No chemotherapy | 550 | PFS 15.3 vs 9.4. ($p = 0.02$) | 20.1 vs 14.7 (HR 0.71, 95% CI 0.55 to 0.92, $p = 0.009$) |
| CONKO 001 Oettle et al. (2007) | Gemcitabine vs Observation | 368 | Median DFS 13.4 vs 6.9 ($p < 0.001$) | 22.1 vs 20.2 ($p = 0.06$) |
| ESPAC 3 Neoptolemos et al. (2010) | 5FU/LV vs Gemcitabine | 1088 | | 23 vs 23.6 (HR 0.94, 95% CI 0.81 to 1.08, $p = 0.39$) |

***Abbreviations:*** CI, confidence interval; CONKO, charite ONKOlogie; DFS, disease free survival; ESPAC, European Study Group for Pancreatic Cancer; 5FU, fluorouracil; HR, hazard ratio; LV, leucovorin; PFS, progression-free survival.

**TABLE 93-2 Selected Phase III Studies Evaluating Chemotherapy Treatment in Advanced Pancreatic Cancer**

| Study | Comparator Arm | Patient Number | Survival | |
|---|---|---|---|---|
| | | | PFS (months) | Median survival (months) |
| Moore M et al. (2007) | Gemcitabine vs Gemcitabine + erlotinib | 569 | 3.55 vs 3.75 (HR 0.77, 95% CI 0.64 to 0.92, $p = 0.004$) | 5.91 vs 6.24 (HR 0.82, 95% CI 0.69 to 0.99, $p = 0.038$) |
| GEM-CAP Cunningham et al. (2009) | Gemcitabine vs Gemcitabine + capecitabine (GEM-CAP) | 533 | 3.8 vs 5.3 (HR 0.78, 95% CI 0.66 to 0.93, $p = 0.004$) | 6.2 vs 7.1 (HR 0.86, 95% CI 0.72 to 1.02, $p = 0.08$) |
| GEM-CAP meta-analysis Cunningham et al. (2009) | Gemcitabine vs GEM-CAP | 935 | | Overall survival in favor of GEM-CAP (HR 0.86, 95% CI 0.75 to 0.98, $p = 0.02$) |

revealed no survival difference between the two drugs. However, the safety profile of adjuvant gemcitabine, with respect to the incidence of stomatitis and diarrhea, was superior to 5FU/FA.

A different treatment strategy using adjuvant 5FU based CRT following gemcitabine as advocated by the Radiation Therapy Oncology Group (RTOG) 97-04 trial is preferred in the United States. This approach may be most beneficial in patients with bulky tumors involving the pancreatic head, and in patients with R1 resection.

**INOPERABLE LOCALLY ADVANCED DISEASE** Approximately 30% of patients present with locally advanced unresectable but nonmetastatic pancreatic carcinoma. The median survival with gemcitabine is 9 months, and patients who respond to or achieve stable disease after 3–6 months of gemcitabine may derive benefit from consolidation radiotherapy.

**METASTATIC DISEASE** Approximately 60% of patients with pancreatic cancer present with metastatic disease. Patients with poor performance status do not benefit from chemotherapy. Gemcitabine is the standard treatment with a median survival of 6 months and a 1-year survival rate of only 20%. The toxicities associated with gemcitabine need to be weighed against the potential benefits of treatment.

Adding other drugs to gemcitabine to improve outcome has been generally unsuccessful with the exception of erlotinib, an oral HER1/EGFR tyrosine kinase inhibitor. The combination of erlotinib with gemcitabine resulted in an improved 1-year survival compared with gemcitabine alone (23% versus 17%, $p = 0.023$) (Table 93-2). Capecitabine, an oral fluoropyrimidine, has been combined with gemcitabine (GEM-CAP) in a phase III trial that showed an improvement in response rate and progression-free survival over single-agent gemcitabine, but no survival benefit. However, pooling of two other randomized controlled trials with this trial in a meta-analysis resulted in a survival advantage with GEM-CAP.

A trial in good performance status patients with metastatic pancreatic cancer showed improved survival with the combination of 5FU/FA, irinotecan and oxaliplatin (FOLFIRINOX) compared with gemcitabine, but with increased toxicity. Nab-paclitaxel (Abraxane), an albumin bound nano-particle formulation of paclitaxel, given with gemcitabine also shows promising activity.

## FUTURE DIRECTIONS

The early detection and future treatment of pancreatic cancer relies on an improved understanding of molecular pathways involved in the development of this disease. This will ultimately lead to the discovery of novel agents, and the identification of patient groups who are likely to benefit most from targeted therapy.

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# EXHIBIT 11

FOCUS REVIEW

*Endocrine-Related Cancer* (2012) **19** F9–F26

# Diabetes and pancreatic cancer

*YunFeng Cui*[1,2]* *and Dana K Andersen*[1]*

Department of Surgery, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[1]Department of Surgery, Nankai Clinical School of Medicine, Tianjin Nankai Hospital, Tianjin Medical University, Tianjin, China

(Correspondence should be addressed to D K Andersen who is now at Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building DEM2, Room 659, 6707 Democracy Boulevard, Bethesda, Maryland 20892, USA; Email: andersendk@niddk.nih.gov)

*(Y Cui and D K Andersen contributed equally to this work)

## Abstract

Epidemiological studies clearly indicate that the risk of pancreatic cancer (PC) is increased in diabetic patients, but most studies focus on overall diabetes or type 2 diabetes mellitus (T2DM), and there are few studies on the risks of type 1 and type 3c (secondary) diabetes. Possible mechanisms for increased cancer risk in diabetes include cellular proliferative effects of hyperglycemia, hyperinsulinemia, and abnormalities in insulin/IGF receptor pathways. Recently, insulin and insulin secretagogues have been observed to increase the PC risk, while metformin treatment reduces the cancer risk in diabetic subjects. In addition, anticancer drugs used to treat PC may either cause diabetes or worsen coexisting diabetes. T3cDM has emerged as a major subset of diabetes and may have the highest risk of pancreatic carcinoma especially in patients with chronic pancreatitis. T3cDM is also a consequence of PC in at least 30% of patients. Distinguishing T3cDM from the more prevalent T2DM among new-onset diabetic patients can be aided by an assessment of clinical features and confirmed by finding a deficiency in postprandial pancreatic polypeptide release. In conclusion, diabetes and PC have a complex relationship that requires more clinical attention. The risk of developing PC can be reduced by aggressive prevention and treatment of T2DM and obesity and the prompt diagnosis of T3cDM may allow detection of a tumor at a potentially curable stage.

*Endocrine-Related Cancer* (2012) **19** F9–F26

## Introduction

Pancreatic cancer (PC) is one of the most lethal malignant diseases due to the high rate of advanced stage disease at diagnosis and the lack of any effective medical therapy (Ko & Tempero 2009). The overall incidence of the disease has increased over the past few decades such that over 265 000 people worldwide are diagnosed annually (Jemal *et al.* 2011). Five-year survival after surgical resection has slowly risen to about 20%, owing to better selection of surgical candidates and some modest improvements in adjuvant therapy, but only 10–15% of patients are candidates for resection, and more than 95% of all patients will succumb to their illness within 2 years of diagnosis (Edwards *et al.* 2005). This high mortality rate confers PC as the fourth leading cause of cancer-related deaths in the USA currently (Jemal *et al.* 2010). With the continuing decline in mortality rates of cancers of the lung, colon, breast, and prostate due to the combined effects of widespread screening, smoking cessation, and more effective therapy, it is projected that pancreas cancer will become the leading cause of cancer-related deaths in the USA by 2050 (Siegel *et al.* 2012).

The etiology of PC is complex and poorly understood. Therefore, the identification of risk factors, especially those that are modifiable through medication or behavioral change, is important for preventing the development and progression of PC. Risk factors for PC include family history, smoking, obesity, chronic pancreatitis (CP), and diabetes mellitus (DM). The recent increase in the prevalence of type 2 DM (T2DM) is thought to have contributed to a parallel rise in the incidence of PC. Roughly half of all PC patients are found to have DM at the time of diagnosis, and roughly half of the DM that is present at the time of PC diagnosis is of new onset having developed over


DOI: 10.1530/ERC-12-0105
1351–0088/12/019–F9 
*Online version via http://www.endocrinology-journals.org*

2–3 years preceding the diagnosis of PC. This new-onset DM is therefore thought to be secondary, or T3cDM. The association between PC and DM has been investigated extensively, but the causal relationships have yet to be fully elucidated, in part due to difficulties in distinguishing T2DM from T3cDM.

In this review, we highlight the important recent studies and discuss the available evidence concerning the possible mechanisms that are involved in the etiological role of DM in the development of PC, the effects of antidiabetic therapy on the risk of PC, and a strategy for distinguishing T3cDM from T2DM so as to identify the patient with early and indolent PC.

## Diabetes (and obesity) as a cause of PC

### The risk of PC is increased in T1DM, T2DM, and T3cDM

It has long been known that PC is associated with DM, and recent studies have revealed that about 85% of patients diagnosed with PC have impaired glucose tolerance or frank DM (Pannala *et al.* 2008; Fig. 1). DM is a group of metabolic disorders characterized by hyperglycemia. The three most common subtypes of DM differ greatly in their metabolic and hormonal characteristics, however (Table 1; Cui & Andersen 2011). T1DM is associated with a profound or absolute deficiency of endogenous insulin secretion and an absolute requirement for exogenous insulin administration. Hyperglycemia and hyperinsulinemia coexist in T2DM due to insulin resistance in peripheral tissues usually in association with obesity. T3cDM is associated with benign and malignant disease of the exocrine pancreas, including acute and CP of any etiology, pancreatic neoplasms, pancreatic trauma, pancreatic resection, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, and pancreatic agenesis and is characterized by a severe deficiency of all pancreatic glucoregulatory hormones (American Diabetes Association 2011, Cui & Andersen 2011).

Epidemiological studies have demonstrated that DM is a risk factor for multiple forms of malignancy including PC (Wideroff *et al.* 1997, Calle *et al.* 2003, Huxley *et al.* 2005). A recent meta-analysis of 35 cohort studies concluded that a twofold risk of pancreatic malignancy exists in diabetic patients (Ben *et al.* 2011). DM was associated with an increased relative risk (RR) of PC (RR = 1.94; 95% confidence interval (95% CI): 1.66–2.27), with significant evidence of heterogeneity among the studies surveyed ($P < 0.001$, $I^2 = 93.6\%$). Subgroup analyses revealed that the increased risk of PC was independent of geographic location, sex, study design, alcohol consumption, body mass index (BMI), and/or smoking status. In addition, the risk of PC correlated negatively with the duration of DM, with the highest risk of PC found among patients with DM diagnosed within < 1 year. This finding implies that many of the diabetic subjects had PC-induced DM (T3cDM), but the type of DM was not identified in most epidemiological studies.

A meta-analysis of three recent studies in which 2192 PC patients were compared with 5113 controls revealed a 1.8-fold increase in risk of PC associated with T2DM, although many of the patients classified as

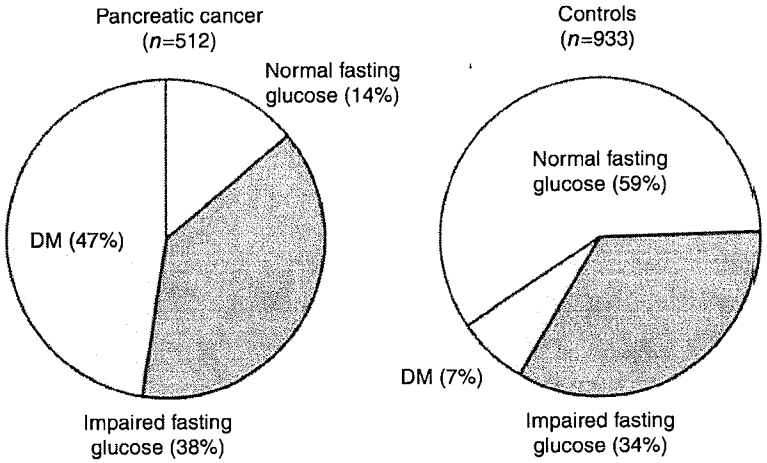


**Figure 1** Distribution of fasting blood glucose among pancreatic cancer cases and controls. Normal fasting glucose, ≤99 mg/dl; impaired fasting glucose, 100–125 mg/dl; diabetes (DM), ≥126 mg/dl. Reproduced, with permission, from Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM & Chari ST 2008 Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* **134** 981–987. Copyright 2008 AGA Institute.

**Table 1** Clinical and laboratory findings in types of diabetes mellitus

| Parameter | Type 1 IDDM | Type 2 NIDDM | Type 3c Pancreatogenic |
|---|---|---|---|
| Ketoacidosis | Common | Rare | Rare |
| Hyperglycemia | Severe | Usually mild | Mild |
| Hypoglycemia | Common | Rare | Common |
| Peripheral insulin sensitivity | Normal or increased | Decreased | Increased |
| Hepatic insulin sensitivity | Normal | Normal or decreased | Decreased |
| Insulin levels | Low | High | Low |
| Glucagon levels | Normal or high | Normal or high | Low |
| PP levels | Normal or low (late) | High | Low |
| GIP levels | Normal or low | Normal | Low |
| GLP1 levels | Normal | Normal or low | Normal or high |
| Typical age of onset | Childhood or adolescence | Adulthood | Any |

IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; PP, pancreatic polypeptide; GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon-like peptide 1. Modified, with permission, from Slezak LA & Andersen DK 2001 Pancreatic resection: effects on glucose metabolism. *World Journal of Surgery* **25** 452–460. Copyright 2001 International Society of Surgery.

T2DM likely harbored T3cDM, which became evident close to the time of diagnosis of the cancer (Li *et al.* 2011). Finally, a recent cohort study comparing 110 919 DM subjects and 211 695 controls provides strong support for an etiological role of T2DM and hyperinsulinemia in the pathogenesis of PC (Yacoub *et al.* 2011). The DM cohort had 124 PCs developed during 0.558 million person-years (MPY) of follow-up (222 PCs/MPY), whereas the control cohort had 140 PCs developed during 1.299 MPY of follow-up (108 PCs/MPY). Stratified Cox regression of PC incidence yielded a hazard ratio (HR) of 2.17 (95% CI: 1.70–2.77) for T2DM compared to controls. So the risk of developing PC is clearly although modestly increased (about twofold) in the presence of long-standing, mostly T2DM.

Genetic studies have also provided insights underlying the association of DM and PC. Pierce *et al.* (2011) examined the 37 risk alleles of T2DM and found two that showed nominally significant positive associations with PC risk (FTO rs8050136 per allele odds ratio (OR) = 1.12; 95% CI: 1.02–1.23; MTNR1B rs1387153 OR = 1.11; 95% CI: 1.00–1.23), and the glucose-raising allele of MADD rs11039149 was associated with increased risk of PC (OR = 1.14; 95% CI: 1.03–1.27). Prizment *et al.* reported that glucokinase regulator (GCKR) rs780094, a single-nucleotide polymorphism related to T2DM, may be associated with PC risk. In a multivariate-adjusted model, a significant association was observed only for rs780094 in the GCKR gene: ORs for PC were 1.00 for the TT genotype, 1.35 (95% CI: 0.71–2.58) for the CT genotype, and 2.14 (95% CI: 1.12–4.08) for the CC genotype ($P = 0.01$), which did not change after the adjustment for the presence of DM (Prizment *et al.* 2012).

There are few studies that specifically address cancer incidence in T1DM patients. A cohort study evaluating cancer incidence in nearly 30 000 Swedish T1DM patients diagnosed in the period 1965–1999 identified 355 cases of cancer, which equated to a standardized incidence ratio of 1.2 (95% CI: 1.0–1.30) compared with the general Swedish population (Zendehdel *et al.* 2003). In contrast to these modest findings, a meta-analysis including three cohort studies and six case–control studies has found that the RR for PC was doubled in T1DM patients and 'young-onset' diabetics in comparison with nondiabetics (Stevens *et al.* 2007).

T3cDM has emerged as a major subset of the total population of DM and harbors the highest risk of PC especially in patients with T3cDM secondary to CP (Cui & Andersen 2011). Persons with any form of CP are at increased risk of developing PC, and Lowenfels *et al.* (1993) observed that the risk is cumulative over the course of CP, such that 4–5% of patients develop PC over the course of 20 years, a risk that is 10–20 times greater than the general population. In a case–control study in which 823 PC patients and 1679 controls were surveyed from centers in Australia, Canada, The Netherlands, and Poland, the risk of PC was seen to be increased (RR 4.7) for subjects with a history of pancreatitis (not otherwise defined), although was increased only among alcohol drinkers (RR 7.5) and not among teetotalers (RR 0.57; Maisonneuve *et al.* 2010; Fig. 2). A recent cohort study in Taiwan showed that in addition to age, CP (HR = 19.40), gallstones (HR = 2.56), and hepatitis C infection (HR = 3.08) were significant factors predicting PC; patients with concurrent DM and CP had a dramatically elevated risk of developing PC (HR = 33.52), compared with subjects without these comorbidities (Liao *et al.* 2012).

### Obesity as a risk factor for PC

In 2003, Calle *et al.* (2003) examined the American Cancer Society database to assess the possible role of

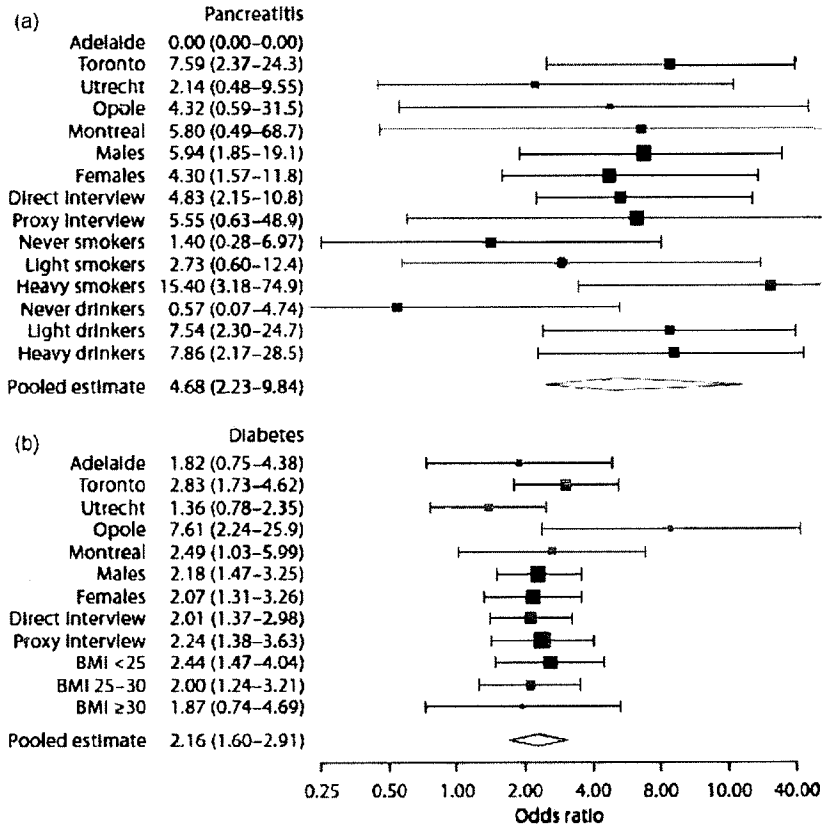


**Figure 2** Risk of pancreatic cancer based on the history of pancreatitis or diabetes. The odds ratio of subsequent pancreatic cancer based on the medical history of pancreatitis (upper panel) or diabetes (lower panel) in 823 patients with pancreatic cancer and 1679 controls surveyed in Australia (Adelaide), Canada (Toronto and Montreal), The Netherlands (Utrecht), and Poland (Opole). Reproduced, with permission, from Maisonneuve P, Lowenfels AB, Bueno-de-Mesquita HB, Ghadirian P, Baghurst PA, Zatonski WA, Miller AB, Duell EJ, Boffetta P & Boyle P 2010 Past medical history and pancreatic cancer risk: results from a multicenter case–control study. *Annals of Epidemiology* **20** 92–98. Copyright 2010 Elsevier Inc.

obesity on the risk of cancer. In their cohort of over 900 000 individuals, massive obesity (BMI >40) was associated with a 50–60% increased death rate from cancers of the pancreas, liver, kidney, colon and rectum, esophagus, non-Hodgkins lymphoma, and multiple myeloma over a 16-year period. The greatest effects were seen in liver cancer (RR 4.52 for men and 1.68 for women), colorectal cancer (RR 1.84 for men and 1.46 for women), and PC (RR 1.49 for men and 2.76 for women). Over 80% of T2DM patients are obese and studies on the obesity–PC association are influenced by the high prevalence of obesity in T2DM patients and by the high percentage of T2DM that is undiagnosed. Recent epidemiological studies have demonstrated that a high BMI is positively associated with an increased risk of many common cancers independent of the coexistence of T2DM (Teucher *et al.* 2010), and a high BMI has been identified as an independent risk factor for PC (Michaud *et al.* 2001, Silverman 2001, Gumbs 2008, Arslan *et al.* 2010). More recently, large prospective cohort studies with a long duration of follow-up have been conducted in the USA showing a positive association between high BMI and the risk of PC (adjusted RR 1.13–1.54; Jiao *et al.* 2010, Johansen *et al.* 2010), suggesting the role of obesity and overweight as conferring a higher risk for the development and eventual death due to PC. Among the many possible mechanisms involved, hyperinsulinemia, diet and nutritional factors, and other hormone abnormalities have been suggested as causal factors.

Reduced caloric intake and physical exercise have both been shown to reduce the risk of PC (Michaud *et al.* 2001, Silverman 2001), and studies on the effects of bariatric surgery are also consistent with a reduction in PC risk after weight loss. In 2007, the Swedish Bariatric Surgery Trial reported a 38% reduction in cancer-related deaths compared with nonoperated controls of similar BMI (Sjöström *et al.* 2007), and a significant reduction in cancer-related medical care was documented in a study of 1035 bariatric surgery

patients compared to 5746 morbidly obese controls reported by Christou *et al.* (2008). In a similar but larger study, Adams *et al.* (2009) found a lower incidence of obesity-related cancers, defined as esophageal, colorectal, pancreas, liver, gallbladder, breast, and uterine cancers, in addition to non-Hodgkin's lymphoma, leukemia, and multiple myeloma in 6596 gastric bypass patients compared with 9442 morbidly obese control subjects. As with the studies by Sjöström *et al.* and Christou *et al.*, the incidence of PC, *per se*, was too low for valid statistical analysis. Although the mechanisms of risk-reduction remain speculative, the successful treatment of morbid obesity (and concomitant T2DM in about half the subjects) appears to clearly reduce the risk of malignancy and may reduce the incidence of PC.

### Proliferation rates of pancreatic ductal endothelium in diabetes and obesity

The effects of DM and obesity on pancreatic ductal pathology were recently studied by Butler *et al.* (2010), who examined the expression of the neoplastic markers cytokeratin and Ki67 in pancreatic ductal epithelia from 45 human autopsy and nine surgical pathology specimens. In autopsy specimens obtained from obese nondiabetic individuals, pancreatic duct replication was seen to be increased tenfold compared with lean nondiabetics. In lean diabetics, duct epithelial replication was increased fourfold compared with lean nondiabetic subjects. These results indicate the independent effects of obesity and long-standing diabetes on the replication rate in pancreatic ductal cells and presumably therefore on the likelihood of the development of pancreatic exocrine neoplasia (Fig. 3). Markers of pancreatic ductal replication were increased synergistically in obese diabetic subjects. When surgical specimens of CP or nontumor tissue adjacent to PC were examined, even higher rates of the expression of replication markers were seen. These findings support the epidemiological studies that have identified CP, DM, and obesity as contributory to oncogenesis in the pancreas.

### Proposed mechanisms of diabetes-related pancreatic carcinogenesis

Although epidemiological studies clearly indicate that DM is positively associated with an increased risk of PC, the molecular mechanism(s) of diabetes-related oncogenesis have not been fully elucidated. Insulin resistance and induced compensatory hyperinsulinemia are widely considered to be likely mechanisms to explain the association of DM and PC (Magruder *et al.* 2011, Li 2012). Several epidemiological studies have

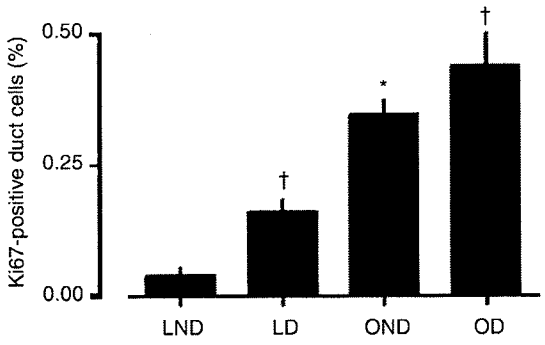


**Figure 3** Number of cytokeratin-staining pancreatic ductal cells positive for Ki67, a marker of cellular replication, in autopsy-harvested pancreata. LND, lean nondiabetic patients ($n=9$); OND, obese nondiabetic patients ($n=11$); LD, lean with type 2 diabetes ($n=12$); OD, obese with type 2 diabetes ($n=13$). Data are presented as mean±S.E.M. *$P<0.0001$, LND vs OND. †$P<0.001$, LD vs OD and LND vs LD. Reproduced, with permission, from Butler AE, Galasso R, Matveyenko A, Rizza RA, Dry S & Butler PC 2010 Pancreatic duct replication is increased with obesity and type 2 diabetes in humans. *Diabetologia* **53** 21–26. Copyright 2009 The Authors.

shown that insulin resistance status, characterized by hyperinsulinemia, is associated with an increased risk for a number of malignancies, including carcinomas of the breast, prostate, colon, and kidney. Hyperglycemia has also been shown to be a risk factor for PC. Batty *et al.* (2004) in England found evidence for a graded dose–response relationship between fasting glucose and the development of pancreatic or liver cancer resulting in mortality. Jee *et al.* (2005) similarly found a positive linear relationship between fasting glucose and the risk of developing PC across all categories of obesity in a cohort analysis of 1 298 385 Korean patients. In a study of 29 133 Finnish smokers followed for over 10 years, Stolzenberg-Solomon *et al.* (2005) found that hyperglycemia, hyperinsulinemia, and insulin resistance were each associated with an increased risk of PC. The HR for PC for each entity did not increase significantly until more than 10 years of follow-up, suggesting that long-standing impairments were necessary for the development of PC.

Detailed reviews of these insulin-related mechanisms are provided by Pollak (2008) and Rozengurt *et al.* (2010). The insulin-like growth factor receptor 1(IGF1R), a tyrosine kinase receptor for IGF1 and 2, has been well documented in cell culture, animal studies, and humans to play a role in malignant transformation, progression, protection from apoptosis, and metastasis in a variety of malignancies. In addition, the hormone insulin and its tyrosine kinase receptor (insulin receptor (IR)) have been documented both *in vitro* and *in vivo* to play a key role in cancer biology (Frasca *et al.* 2008). Chronic hyperinsulinemia is a

possible factor favoring cancer initiation and/or progression in diabetic patients due to the mitogenic effect of insulin. Insulin/IGF1 could activate the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway by activation of IR substrates 1–4, which contribute to the development of cancers including PC (Kornmann *et al.* 1998). Recent reports indicate that IR is overexpressed in several human malignancies and one of the two IR isoforms (IR-A) is especially overexpressed in pancreatic adenocarcinoma. The IRs expressed in malignant tissue also have the capacity to form a hybrid receptor with the IGF1R (Belfiore 2007). By binding to hybrid receptors, insulin may stimulate specific IGF1R signaling pathways, which mediate cell proliferation, inhibition of apoptosis, and growth (Fig. 4). Furthermore, Han *et al.* (2011) recently found that high glucose promotes PC cell proliferation via the induction of epithelial growth factor (EGF) expression and transactivation of the EGF receptor.

In addition to activation of receptors linked to proliferative and anti-apoptotic pathways, other possible mechanisms have also been suggested as important mediators of pancreatic carcinogenesis. The DM and obesity-related effects on PC development may be mediated by oxidative stress and induced inflammatory responses (Li 2012). Inflammatory responses to external stimuli can accelerate proliferative and repair processes, and obesity itself may activate inflammatory signaling pathways (Greer & Whitcomb 2009, Gallagher & LeRoith 2010). Proinflammatory cytokines released from adipose tissue, known as adipokines, can promote angiogenesis, tumor progression, and metastasis (van Kruijsdijk *et al.* 2009).

## Evidence for increased risk of PC with insulin, insulin secretagogues, and incretin-based treatment

Although the mortality attributable to cancer in DM is overshadowed by that due to cardiovascular disease, emerging data from basic and epidemiological studies suggest that insulin therapy may confer an added risk for cancer, perhaps mediated by signaling through the IGF1R (Azar & Lyons 2010). In 2000, Ding *et al.* (2000) found that physiological concentrations of insulin increased PC cell proliferation as well as glucose use by activating MAP kinase, PI3 kinase, and GLUT1 expression. In 2003, Bonelli *et al.* (2003) in Italy reported a case–control study in which the effect of

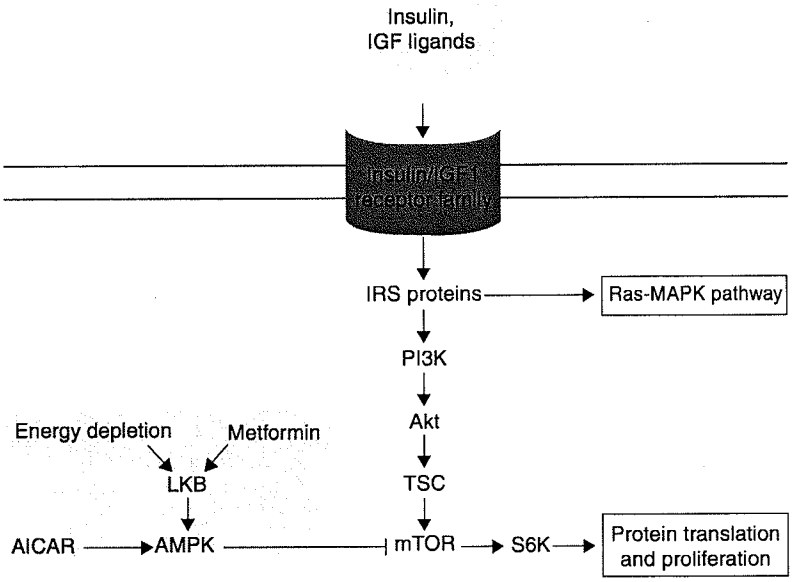


**Figure 4** Insulin, insulin-like growth factor 1 (IGF1), and IGF2 mediation of translation and proliferation, and the effects of metformin on these pathways. Phosphorylation of insulin receptor substrate (IRS) proteins by insulin/IGF receptors activates phosphatidylinositol-3 kinase (PI3K) and the Ras–MAP-kinase signaling network. PI3K activates Akt that regulates protein synthesis and replication through the intermediate mammalian target of rapamycin (mTOR). Energy depletion or the drug metformin results in activation of AMP protein kinase (AMPK) through the intermediate liver kinase B1 (LKB). In the liver, AMPK activation results in diminished hepatic glucose production, which results in lower levels of circulating insulin. In the pancreas and elsewhere, AMPK inhibits mTOR signaling. Modified, with permission, from Magruder JT, Elahi D & Andersen DK 2011 Diabetes and pancreatic cancer: chicken or egg? *Pancreas* **40** 339–351. Copyright 2011 American Pancreatic Association and Japan Pancreas Society.

type of treatment for DM on the subsequent development of PC was assessed. Two hundred and forty four patients with documented pancreatic carcinoma and 459 controls were assessed to determine whether insulin therapy or non-insulin therapy affected the subsequent rate of PC development. These investigators found that although DM was associated with a 2.86-fold increase in the risk for PC, the risk increased to 6.49-fold for those treated with insulin, compared with 2.12-fold for those treated with oral hypoglycemic agents. Furthermore, although the duration of insulin treatment had no effect on the high-risk ratio (RR), longer duration of oral hypoglycemic therapy was associated with a lower RR for the development of PC. These findings were corroborated in 2006 by Bowker *et al.* (2006) who also found increased cancer-related mortality in T2DM patients treated with insulin or sulfonylureas. In the 2010 multinational case–control study by Maisonneuve *et al.* (2010), a history of DM conveyed an increased RR for PC overall (2.16), which was 6.68 for those whose history of DM started within 1 year of the diagnosis of cancer, falling to 1.28 for those whose diabetic history had existed for more than 10 years. In addition, the type of treatment for the DM was found to have a differential effect, with those who had been treated with insulin having an RR of 3.54, while those who had been treated only with oral agents having an RR of 1.78. These findings confirmed those of Bonelli *et al.* who similarly found a higher risk associated with insulin treatment than with non-insulin therapy. The higher risk seen with insulin treatment in the case–control studies of Maisonneuve *et al.* and Bonelli *et al.* may reflect a direct effect of insulin on tumor cell proliferation as insulin therapy would also be expected to produce periods of hyperinsulinemia. In addition, however, other factors may have contributed to the results, including length of treatment and the degree of hyperglycemia present, both of which would be expected to be greater in insulin-requiring patients. Carstensen *et al.* (2012) recently analyzed the effect of diabetes and diabetic therapy on cancer incidence in the Danish health system over a 27-year period and noted that the adverse effects of insulin treatment were quite modest. Therefore, caution has been advised in the acceptance of a cancer-promoting effect of insulin until further data are available (Gerstein 2010, Giovannucci *et al.* 2010, Hernandez-Diaz & Adami 2010).

Insulin therapy has also been associated with a greater than expected incidence of breast cancer and other malignancies (Home & Lagarenne 2009, Jonasson *et al.* 2009), however, and insulin secretagogues have similarly been implicated in an increased incidence of PC. Case–control studies indicate an increased risk of cancer overall in T2DM patients treated with sulfonylureas (Bowker *et al.* 2006, Monami *et al.* 2009), and studies of PC in particular indicate that sulfonylurea therapy confers an increased risk (Currie *et al.* 2009, Li *et al.* 2009).

Incretin-based therapies (glucagon-like peptide-1 (GLP1) analogues and inhibitors of didpeptidyl peptidase-IV, the enzyme that metabolizes GLP1) are the newest form of insulin secretagogue treatment of T2DM. No long-term epidemiological studies have yet been reported of their effect on the incidence of PC due to the relatively short period of clinical availability of these agents. However, laboratory studies suggest an adverse effect of these agents on the development of pre-neoplastic or malignant lesions of the pancreas, possibly related to the growth-promoting effects of GLP1 and its analog exendin-4. Matveyenko *et al.* (2009) described the effects of sitagliptin, a DDP-IV inhibitor, on pancreatic ductal cell proliferation and β-cell mass in the human islet amyloid polypeptide (HIP) transgenic model of T2DM in rats. Sitagliptin was seen to induce β-cell replication, β-cell apoptosis, pancreatic ductal metaplasia, and a fourfold increase in duct cell proliferation, all effects that were blocked by concurrent metformin administration (Fig. 5).

Gier *et al.* (2012) recently reported that the GLP1 analog exendin-4 increased duct cell replication and increased the development of dysplastic pancreatic intraepithelial neoplasia (PanIN) lesions in a rat model in which activated $Kras^{G12D}$ was induced. These investigators found that pancreatic duct glands (thought to be precursors of PanINs) in both rats and humans contain GLP1 receptors and are increased by treatment with exendin-4.

GLP1 and its analogs have been shown to increase expression of the transcription factor pancreatic–duodenal homeobox-1 (PDX1; Perfetti *et al.* 2000, Stoffers *et al.* 2000). PDX1 is critical for normal pancreatic development and has been shown to be overexpressed in PC (Koizumi *et al.* 2003, Wang *et al.* 2005). Furthermore, PDX1 increases cell proliferation, invasion, and colony formation of transformed cell lines *in vitro* and stimulates PC formation in severe combined immunodeficiency (SCID) mice, thereby fulfilling criteria as an oncogene (Liu *et al.* 2011). The gene *NR5A2* (also known as LRH1) has been identified as a PC susceptibility gene (Petersen *et al.* 2010) and is a target gene of PDX1 expression (Annicotte *et al.* 2003). PDX1-expressing endocrine cells can be transformed into a malignant, ductal cell phenotype after induction of pancreatitis by cerulein in mice (Gidekel Friedlander *et al.* 2009), which supports the epidemiological findings of a striking association of CP with the

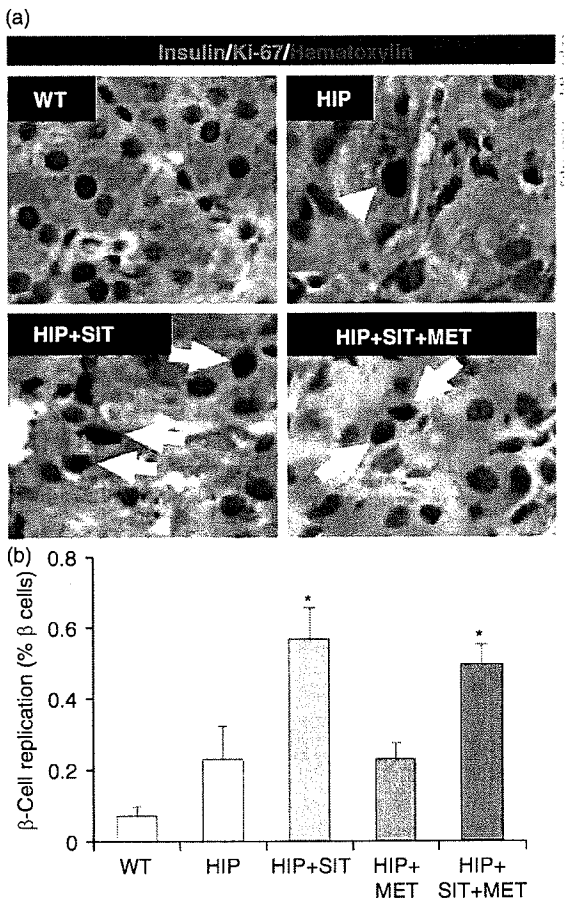


**Figure 5** Effects of sitagliptin and metformin on β-cell replication. (Panel a) Example of islets stained for insulin (pink), the replication marker Ki67 (brown), and nuclear stain hematoxylin (blue) in wild-type (WT) and transgenic rats expressing human islet amyloid polypeptide (HIP), a model of type 2 diabetes, treated with sitagliptin (200 mg/kg per day; HIP+SIT) or metformin (200 mg/kg per day; HIP+MET), or both (HIP+SIT+MET) for 12 weeks. (Panel b) Frequency of β-cell replication in WT rats ($n=7$), HIP rats ($n=8$), HIP rats treated with SIT ($n=8$), HIP rats treated with MET ($n=9$), or HIP rats treated with both SIT and MET ($n=8$). *$P<0.05$ vs WT, HIP, and HIP+MET groups. Arrows indicate Ki67-positive cells. Reproduced, with permission, from Matveyenko AV, Dry S, Cox HI, Moshtaghian A, Gurlo T, Galasso R, Butler AE & Butler PC 2009 Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. *Diabetes* **58** 1604–1615. Copyright 2009, American Diabetes Association.

development of PC (Greer & Whitcomb 2009). These findings suggest that Kras activation, either by genetic or nongenetic (inflammatory) events, may therefore activate neoplastic transformation within the pancreas to PDX1-expressing islet and/or ductal cells. Agents that increase PDX1 expression, such as GLP1 and its analogs, may therefore facilitate this process.

Most recently, Elashoff *et al.* (2011) examined the database of adverse outcomes reported to the US Food and Drug Administration and discovered that compared with other antidiabetic therapies, the use of sitagliptin or the GLP1 analog exenatide was associated with a two- to three-fold increase in the reporting incidence of PC. Although subject to multiple methodological limitations, these findings nevertheless raise concerns regarding an increased risk for pancreatitis and PC with GLP1-based therapy. Further epidemiological studies are clearly needed to define the possible hazards of incretin-based antidiabetic therapy, particularly in patients with T3cDM due to CP (Cui & Andersen 2011).

## Evidence for decreased PC incidence in patients treated with metformin

Although insulin and insulin secretagogue therapy is associated with an increased risk of PC, numerous clinical studies have demonstrated that the administration of metformin in DM patients exhibits a protective effect that is manifested by a decreasing incidence of different tumors and an improved prognosis of patients with cancer. Metformin has been widely used for the treatment of T2DM for almost 50 years, and its effectiveness has been attributed to enhanced sensitivity to insulin, rather than to an insulinotropic action. Its safety and efficacy are so well established that it is recommended as the first line of therapy for T2DM (Nathan *et al.* 2009). Evans *et al.* (2005) evaluated metformin use in diabetics who were admitted to hospital with a diagnosis of cancer between 1993 and 2001 in Tayside, Scotland, and compared this cohort with diabetic controls who were not admitted for cancer. They found that any exposure to metformin was associated with a significant reduction in cancer risk (RR=0.77). The same group subsequently examined the database of all diabetic patients in the region and compared outcomes based on the national registry of cancer deaths (Libby *et al.* 2009). When the outcome of 4804 metformin users was compared with 4085 nonusers, a reduced risk (RR 0.63) for cancer mortality was found among diabetic patients treated with metformin, whereas a (nonsignificantly) increased risk of cancer mortality was seen among insulin and sulfonylurea users. Li *et al.* (2009) analyzed 978 patients with PC, including 259 diabetics, and 863 controls, including 109 diabetics, to assess the effects of diabetes treatment on the risk of PC. They found that whereas insulin treatment was associated with an increased risk (RR 2.78 for insulin users of more than 5 years), metformin therapy was associated with a 70% decreased risk (RR 0.30) for similar long-term users of the drug. The implications

are further supported by a more recent cohort study from Taiwan in which metformin users were found to have a 85% decreased risk of pancreatic malignancy (HR 0.15, 95% CI: 0.03–0.79; Lee *et al.* 2011*b*). Sadeghi *et al.* (2011) performed a retrospective cohort study of 302 patients to investigate the survival benefit of metformin in patients with DM and pancreatic malignancy. They report the median survival to be longer in metformin users when compared with nonusers: 16.6 vs 11.5 months ($P=0.0044$). They also report a 33% decreased risk of death in patients who used metformin compared with those who did not. In addition to studies of its anticancer effects in PC, metformin has also been shown to have anticancer effectiveness in diabetic breast cancer patients (Jiralerspong *et al.* 2009, Chlebowski *et al.* 2012) and in colon cancer patients (Zhang *et al.* 2011).

These clinical studies corroborated the initial findings of Schneider *et al.* (2001) who found a therapeutic effect of metformin in a hamster model of carcinogen-induced PC. In these animals, metformin treatment significantly decreased islet cell hyperplasia and pancreatic ductal proliferation and completely prevented the development of pancreatic adenocarcinoma. Additional evidence showed that metformin can inhibit PC cell growth and proliferation by disrupting the cross talk between insulin/IGF1Rs and G-protein-coupled receptors through the activation of the liver kinase B1–AMP (LKB1–AMP) AMPK pathway, which serves not only to suppress hepatic glucose production and reduce the need for insulin but also inhibits the signaling mechanisms that regulate cellular proliferation (Rozengurt *et al.* 2010). LKB1 is a known tumor suppressor that activates AMPK, a potent inhibitor of mTOR complex 1, which serves as a regulator of protein synthesis and replication (see Fig. 4). Bao *et al.* (2012) found that metformin significantly decreased cell survival, clonogenicity, wound healing capacity, sphere-forming capacity (pancreatospheres), and increased disintegration of pancreatospheres in both gemcitabine-sensitive and gemcitabine-resistant PC cells. Metformin also decreased the expression of cancer stem cell (CSC) markers, CD44, EpCAM, EZH2, Notch1, Nanog, and Oct4 and caused re-expression of miRNAs (let-7a, b, miR-26a, miR-101, and miR-200b,c) that are typically lost in PC. These results suggest that the biological effects of metformin as an antineoplastic agent are mediated through re-expression of miRNAs and decreased expression of CSC-specific genes that are affected by carcinogenesis, and numerous laboratory and clinical studies are now underway to examine the antitumor applications of metformin.

## Diabetes as a consequence (and harbinger) of PC

### The prevalence of diabetes is increased in PC patients

Many cohort and case–control studies indicate that 25–50% of patients with a diagnosis of PC will have developed DM within 1–3 years before their diagnosis of malignancy (Huxley *et al.* 2005, Chari *et al.* 2008). This implies that recent-onset DM associated with PC is caused by pancreatic malignancy and suggests that DM is a biomarker of early-stage PC. The problem is that new-onset DM, *per se*, is not a powerful-enough predictor of PC to stand alone as an indication for radiological or endoscopic screening, as 98% of patients with adult-onset DM will never develop PC (Chari *et al.* 2005*a*). Imaging protocols applied to patients with new-onset DM older than the age of 50 have not been shown to be either practical or reliable as an early detection method based on the studies in Japan (Ogawa *et al.* 2002), France (Damiano *et al.* 2004), and the USA (Chari *et al.* 2005*a*,*b*).

In addition to the frequent development of DM just proximate to the diagnosis of PC, the concept that PC is a cause of new-onset DM is supported by several observations. Patients with premalignant pancreatic lesions from kindreds in which PC is highly prevalent typically have concurrent DM (Brentnall *et al.* 1999). Furthermore, new-onset DM associated with PC has been seen to resolve after the successful resection of the tumor (Permert *et al.* 1993, Fogar *et al.* 1994, Pannala *et al.* 2008; Fig. 6). In laboratory studies, PC-derived cell lines induce hyperglycemia in SCID mice (Basso *et al.* 1995), and a PC-derived S-100A8 N-terminal peptide has been identified as a diabetogenic agent (Basso *et al.* 2006).

Despite vigorous clinical investigation, no biomarker specific for PC-associated DM has been validated, and tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9 are insufficiently sensitive to detect early-stage disease. Permert *et al.* (1994) identified elevated levels of islet amyloid polypeptide (IAPP), a β-cell peptide co-secreted with insulin, as a possible biomarker of PC and demonstrated that PC cells are capable of inducing IAPP release from β-cells (Ding *et al.* 1998), but Chari *et al.* (2001) subsequently showed that IAPP was not sufficiently sensitive to serve as a biomarker of PC. Using microarray analysis, Pfeffer *et al.* (2004) identified connexin 26, a gap junction protein, as being highly overexpressed in PC patients with DM. Using similar methods, Huang *et al.* (2010) identified two upregulated genes in 27 patients with PC-associated DM, vanin-1 and matrix metalloproteinase 9, that

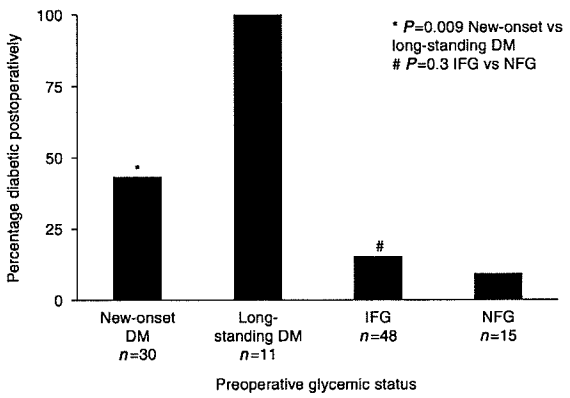


**Figure 6** Prevalence of postoperative diabetes after pancreaticoduodenectomy for pancreatic cancer. Data for patients with new-onset diabetes (2-year duration), impaired fasting glucose (IFG), and normal fasting glucose (NFG) are shown: NFG, 126 mg/dl (7 mmol/l). Whereas postoperative diabetes was seen in all long-standing diabetic patients, and in some patients with IFG and NFG, diabetes resolved in more than 50% of patients with new-onset diabetes despite removal of half of the (β)-cell mass. Reproduced, with permission, from Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM & Chari ST 2008 Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. *Gastroenterology* **134** 981–987. Copyright 2008 AGA Institute.

together showed the best correlation with the diagnosis. No large-scale studies have been reported yet regarding the sensitivity and specificity of these possible biomarkers.

## Pathogenesis of pancreatic carcinoma-associated diabetes

The mechanism(s) responsible for the DM caused by PC are incompletely understood. Defects in insulin sensitivity and insulin secretory capacity have been identified in patients with PC-associated DM, and abnormalities in glucose metabolism in skeletal muscle and liver have been observed *in vitro* as well. These multiple abnormalities suggest that one or more humoral factors are likely involved in PC-associated DM, as reviewed by Pannala *et al.* (2009).

Animal models of carcinogen-induced PC exhibit both hyperinsulinemia (Liu *et al.* 2000) and insulin secretory impairments (Ahren & Andren-Sandberg 1993, Permert *et al.* 2001), which implies that insulin resistance is an early event in PC-associated DM. Impaired sensitivity to insulin has been demonstrated in euglycemic glucose clamp studies and by means of the homeostasis model assessment method in patients with PC-associated DM (Cersosimo *et al.* 1991, Chari *et al.* 2005*a*), which improves after removal of the tumor despite reduced insulin secretory capacity after surgical resection (Permert *et al.* 1993, Pannala *et al.* 2008). Clinical studies on the pathophysiology of PC-associated DM have been confounded, however, by the inability of investigators to document whether the DM exhibited by each PC patient is preexisting T2DM or pancreatogenic (type 3c) DM caused by the tumor.

## Distinguishing T3cDM from T2DM

Recalling that T3cDM is the form of DM that is a consequence of pancreatic exocrine pathology and that T3cDM is in many ways distinct from T2DM (see Table 1), the issue therefore becomes how to feasibly distinguish individuals with T3cDM from the vastly more prevalent T2DM, so as to identify the subset of high-risk patients in whom high-resolution imaging tests might feasibly identify suspicious areas within the pancreatic parenchyma.

A retrospective cohort study of 2122 diabetic patients suggested that PC developed within 3 years after the diagnosis of DM in 1% of the patients who were at least 50-year old (Chari *et al.* 2005*a*). Johnson *et al.* (2011) found that the diagnosis of PC was highest within 3 months following the onset of DM, and Aggarwal *et al.* (2012) showed that the duration of DM before the diagnosis of PC by primary care providers averaged 6.5 months. A study by Lee *et al.* (2011*a*) reported that compared with the control group, PC patients were, on average, older, had more weight loss, lower usual BMI, a greater family history of PC (3.3 vs 0.7%; $P=0.044$), and had a lower family history of DM (13.9 vs 37.4%; $P<0.001$). These authors concluded that PC-associated DM (T3cDM) could be discriminated from new-onset T2DM based on clinical features, such as the lack of a family history of DM, age 65 years or older, recent weight loss of $>2$ kg, or a premorbid or usual BMI $<25$ kg/m$^2$. A definitive diagnosis of T3cDM, however, requires further testing for confirmation in patients who lack a history of pancreatic disease or a family history of PC. Fecal elastase-1 levels $<100$ μg/g strongly suggest pancreatic exocrine impairments (Loser *et al.* 1996), but the most consistent laboratory finding in T3cDM due to any cause is a deficiency of the pancreatic polypeptide (PP) response to ingested nutrients (Cui & Andersen 2011, Magruder *et al.* 2011).

## PP deficiency: a marker of T3cDM

PP is localized predominantly to islets in the ventral portion (head) of the pancreas and is promptly secreted in response to ingested nutrients. PP regulates the expression and availability of hepatic IRs, and hepatic insulin resistance due to PP deficiency is reversed by PP administration in animals and man (Andersen 2007).

T3cDM secondary to cystic fibrosis, CP, pancreatic malignancy, or pancreatic resection is uniformly characterized by a deficiency in the nutrient-stimulated release of PP (Fig. 7) and a defect in hepatic insulin sensitivity (Slezak & Andersen 2001, Cui & Andersen 2011). T2DM, on the other hand, is typically associated with an increase in basal and nutrient-stimulated levels of PP (Glaser *et al.* 1988). Furthermore, healthy elderly subjects with normal glucose tolerance also demonstrate elevations in basal and nutrient-stimulated levels of PP compared with younger subjects (Magruder *et al.* 2011; Fig. 8). Therefore, the discrimination of T3cDM from T2DM is based on the failure of plasma PP levels to increase after nutrient ingestion. Basal levels of PP in PP-deficient subjects are similar to basal levels in normal subjects, so a nutrient stimulus is required to confirm PP deficiency. Glucose ingestion is a relatively weak stimulus for PP release, whereas a mixed nutrient meal is a strong inducer of PP release. A standardized mixed-nutrient stimulus is 8 ounces of a liquid dietary supplement such as Ensure-Plus; peak levels of PP are seen within 30–60 min after ingestion. Studies are currently in progress to establish the prevalence of PP deficiency in PC patients with and without DM, but a diagnosis of new-onset T3cDM based on PP deficiency is a strong indicator that the patient is in a high-risk category for PC and warrants further investigation to identify a pancreatic parenchymal abnormality.

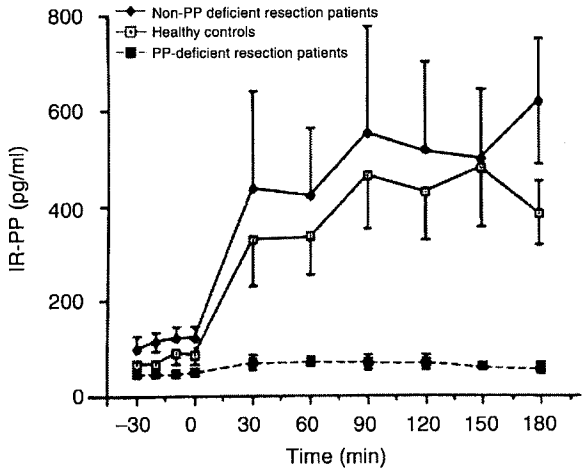


**Figure 7** Serum PP responses to a test meal in eight normal control subjects (open boxes), four non-PP-deficient patients who had recovered from distal pancreatic resection performed for trauma (closed diamonds), and six PP-deficient patients who had recovered from proximal pancreatic resection performed for trauma (closed boxes, broken line). Means±S.E.M. are shown. Reproduced, with permission, from Magruder JT, Elahi D & Andersen DK 2011 Diabetes and pancreatic cancer: chicken or egg? *Pancreas* **40** 339–351. Copyright 2011 Lippincott Williams & Wilkins, Inc.

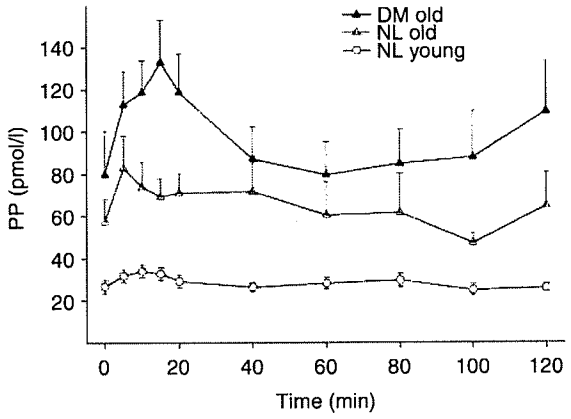


**Figure 8** Serum PP responses to 75 g glucose ingested at time=0 in ten healthy young (age younger than 40 years; NL young), 19 healthy elderly (age older than 65 years) with normal glucose tolerance (NL old), and 21 elderly subjects with T2DM (DM old). Data are shown as mean±S.E.M. Reproduced, with permission, from Magruder JT, Elahi D & Andersen DK 2011 Diabetes and pancreatic cancer: chicken or egg? *Pancreas* **40** 339–351. Copyright 2011 Lippincott Williams & Wilkins, Inc.

## Prevalence of T3cDM

Patients who have a known history of pancreatic disease and who are also diabetic require special surveillance for PC. The most common cause of T3cDM is CP, which harbors a 10- to 20-fold increased risk of PC; the combination of CP and DM increases this risk 33-fold. Unless drug side effects (principally gastrointestinal sensitivity) or a contraindication (such as renal insufficiency) is present, metformin should be prescribed to all T3cDM patients, even if other antidiabetic drugs such as insulin have to be added for adequate glycemic control (Cui & Andersen 2011).

T3cDM had been estimated to account for only 1–2% of all diabetic patients in North America (Ganda 2005) but is known to affect as many as 15–20% of diabetic patients in the Indian and Southeast Asian continents, where tropical or fibrocalcific pancreatitis is endemic (Abu-Bakare *et al.* 1986). In a careful evaluation of almost 2000 diabetic patients referred to an academic medical center in Germany, Hardt *et al.* (2008) discovered that 8% of all diabetic patients harbored T3cDM (Fig. 9). Furthermore, Ewald *et al.* (2011) subsequently showed that nearly half of the T3cDM patients had been previously misdiagnosed as either T1DM (6%) or T2DM (40%). With the advent of improved imaging methods to detect pancreatic pathology, and the availability of a practical screening method to quantify exocrine pancreatic function, previous estimates of the prevalence of T3cDM are now understood to have been spuriously low (Ewald *et al.* 2009).

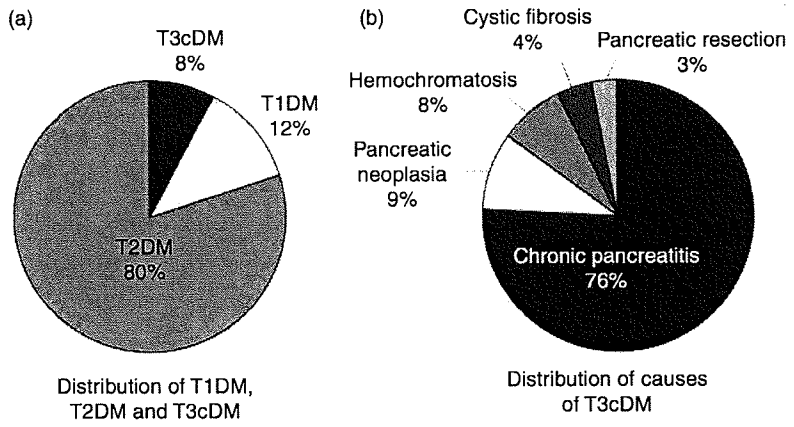


**Figure 9** Distribution of types of diabetes (a) and causes of type 3c (pancreatogenic) diabetes (b) based on the studies of 1922 diabetic patients referred to an academic medical center in Germany. Reproduced, with permission, from Cui Y & Andersen DK 2011 Pancreatogenic diabetes: special considerations for management. *Pancreatology* **11** 279–294. Copyright 2011 S Karger AG. Data from Hardt *et al.* (2008).

In the German cohort study, 78.5% of T3cDM patients had CP as the underlying etiology of their T3cDM. In an older study of 500 patients with CP due to alcoholism, DM developed in 83% within 25 years of the clinical onset of CP, and more than half of the diabetic patients ultimately required insulin therapy (Malka *et al.* 2000). With the increasing prevalence of CP worldwide (Rothenbacher *et al.* 2005), the population of patients at greatest risk for the development of PC is clearly expanding. Therefore, an aggressive approach to the identification, surveillance, and management of patients at high-risk for PC is an important strategy in order to reduce the mortality rate of PC.

### Drugs used to treat PC may cause diabetes

A recently emerging issue is the possible adverse effect on glucose metabolism of anticancer therapies. Cancer patients commonly exhibit hyperglycemic states or DM following glucocorticoid administration (Saylor & Smith 2009). The increasing use of targeted chemotherapy directed against components of the IGF1 pathway may amplify the frequency of anticancer drug-related diabetes. IGF1 and insulin, their receptors, and their intracellular signaling pathways share multiple similarities. Likewise, the biological (metabolic and mitogenic) effects of insulin and IGFs overlap. Hyperglycemia was observed in some patients enrolled in studies with an anti-IGF1R antibody (Haluska *et al.* 2006, Lacy *et al.* 2008). This is likely to be a consequence of a compensatory increase in the circulating concentration of GH after IGF1 blockade, with the consequent increase in GH-induced insulin resistance (del Rincon *et al.* 2007). Hyperglycemia, hypertriglyceridemia, and hypercholesterolemia were also observed in about 20% of patients treated with the mTOR inhibitors (Bellmunt *et al.* 2008). Recent reports also documented increased blood glucose levels in 26% of temsirolimus-treated patients (Bellmunt *et al.* 2008, Malizzia & Hsu 2008). However, tyrosine kinase inhibitor therapy directed at IGF1Rs was associated with less hyperglycemia than IGF1R-blocking antibodies (Pollak 2008). At present, insufficient data are available to assess the possible diabetogenic effects of phosphoinositol-3-kinase and AKT inhibitor therapy.

## Conclusions and clinical recommendations

Epidemiological data clearly demonstrate an etiological link between long-standing T2DM, and probably T1DM, and PC. Successful treatment of T2DM and obesity has been shown to reduce the risk of PC, but treatment with insulin, insulin analogs, and insulin secretagogues increases or maintains the risk. Metformin has been shown to reduce the risk of PC owing to its antidiabetic and antineoplastic actions and should be considered as first-line therapy in all new-onset DM patients over the age of 50. In addition, metformin, as well as lifestyle alterations, have been shown to reduce the incidence of T2DM when administered to obese individuals with impaired glucose tolerance (Knowler *et al.* 2002, Cefalu 2012). Such successful prevention strategies need to be more fully used in order to reverse the increasing incidence of PC.

New-onset DM can be a consequence, and therefore a harbinger, of PC. DM caused by PC is classified as

T3cDM, which occurs in up to 30% of patients with PC. If a new-onset DM patient does not have family history of DM, is aged 65 years or older, or has had a stable BMI $<25$ kg/m$^2$, PC-associated DM (T3cDM) should be considered, especially within 3 months following onset of DM. If the patient has a family history of two or more relatives with PC, high-resolution imaging (preferably computer tomographic scanning followed by endoscopic ultrasound) of the pancreas should be considered to identify suspicious areas within the parenchyma (Brentnall *et al.* 1999).

If no family history of PC is present, T3cDM can be confirmed by documenting the absence of a rise in PP levels after a test meal or liquid mixed-nutrient challenge. Patients with confirmed T3cDM, with or without a history of pancreatic disease, are candidates for periodic high-resolution pancreatic imaging to detect early pathological changes within the pancreas. With an aggressive approach to distinguishing T3cDM from T2DM, many cases of early PC may be able to be identified when curative removal of the tumor is still possible.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

## Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 27 June 2012
Accepted 26 July 2012
Made available online as an Accepted Preprint
27 July 2012